REMARKS

The Claims

Claims 1-9 and 17-25 are pending and stand rejected under 35 U.S.C. § 112 for alleged failure to satisfy the written description and enablement requirements. The previous rejections for alleged indefiniteness have been withdrawn, thus no new claim amendments are presented.

The Rejection under 35 U.S.C. § 112 first paragraph: Written Description.

The claims are drawn to methods to assay for PTH species, using methods that rely on an antibody that recognizes CIP, which is defined as PTH 7-84, but does not bind to CAP. The Examiner based a final rejection of all claims on both Written Description and Enablement grounds. The Applicant is confused about the basis for the written description rejection, especially: it is not clear what basis the Examiner has to distinguish the present claims from the Federal Circuit opinions cited in the previous response. Enzo Biochem. v. Gen-Probe, Inc., 323 F.3d 956, 964 (Fed. Cir. 2002); Noelle v. Lederman, 69 USPQ2d 1508, 1513-14 (Fed. Cir. 2004). These cases and the PTO Guidelines state that the written description requirement for an antibody is satisfied if the application discloses binding of the antibody to a fully characterized antigen. The *Noelle* court summarized as follows:

> Therefore, based on our precedent, as long as an applicant has disclosed a "*fully characterized* antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen.
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> *Noelle,* at 1514.

Here, the description describes an antigen, CIP, by structure: the antigen is precisely described by the sequence of the antigenic peptide. Thus the mandatory authority of the Federal Circuit indicates that the genus of antibodies that bind to this antigen is fully described by their affinity for the fully described antigen.

The description further includes an additional selection criterion: the antibody must not recognize CAP, which is also precisely described by its structure as PTH 1-84. Thus the application uses a second compound to describe a selected sub-genus of the fully described genus of antibodies that bind to the CIP antigen. The description of this sub-genus involves a functional characteristic, but it is directly analogous to that involved in the description of the antibody itself: it relies on the same established structure-function relationship that is sufficient for the description of an antibody by its antigen. The application also provides a screening process that allows the user to identify the selective antibody for the methods of the invention from among the multiplicity of antibodies to CIP that can readily be made by well-known antibody production methods.

The Examiner asserts that the present facts differ from those in *Enzo* and *Noelle*, so those cases are not applicable. However, it is unclear what the Examiner relies on to assert that the standards of *Enzo*, *Noelle*, and indeed the PTO Guidelines, should not apply to this case. It is true that the present application requires an antibody that distinguishes between two molecules; but distinguishing one molecule from others is essentially the normal function of an antibody. The specification provides structures for both the molecule to be recognized (CIP) and the one to be distinguished (CAP). Thus it is unclear why that selectivity requirement makes the case law of the Federal Circuit inapplicable or what different or additional "written description" the Examiner would require in this situation.

The Examiner attempts to distinguish *Enzo* and *Noelle* by saying, "Thus the instant application is different from Enzo and Noelle because the Applicant doesn't have the antibody and the existence of the antibody is unexpected." The Examiner also objected to the "prophetic" language of the application ("Applicant's language is prophetic in nature and does not indicate that such a distinguishing antibody has been produced at the time of filling[sic]."). Finally, the Examiner also states: "Applicant has not shown a single antibody that can discriminate between CIP and CAP and one cannot claim unexpected results without results and one of ordinary skill does not have the knowledge that there is a success and thus one of ordinary skill in the art would not expect to obtain an antibody that discriminates between CIP (7-84) and CAP (1-84)."

However, as the Examiner is well aware, there is no legal requirement for the inventor to reduce an invention to practice prior to filing a patent application. See, e.g., Hyatt v. Boone, 47 USPQ2d 1128, 1130 (Fed. Cir. 1998) ("The filing of a patent application serves as conception and construction reduction to practice of the subject matter described in the application." *Hyatt* resolved an interference in which BOTH parties relied on filing of their applications as constructive reductions to practice: neither was required to demonstrate actual reduction to practice.) *Enzo* and *Noelle* do not impose a 'possession of the antibody' requirement, so the present case is not distinguished from them by that factor: they require a description of the antigen, which the present application provides. The Examiner is not at liberty to impose an extra-statutory "physical possession" requirement on the Applicant, where neither the written description nor the enablement standards includes one. Thus "the Applicant doesn't have the antibody" is not a proper basis for a rejection: it would effectively prohibit the applicant from patenting an invention by imposing a 'physical possession' requirement that has no foundation in U.S. patent law.

The appropriate 'Written Description' question in this situation is not about physical possession. It is provided in the Examiner's comments, where the Examiner states: "The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Thus the important issue is what would the application have conveyed "to one skilled in the relevant art...at the time the application was filed." And emphatically, as just discussed, 'possession of the claimed invention' does NOT refer to possession of any physical embodiment thereof: the applicant is not required to show physical possession of the antibody claimed. (Indeed, the courts often state that the written description requirement exists to put the public "in possession of the claimed invention." See, e.g., Vas-Cath v. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991).)

The heart of the Examiner's rejection apparently relates to the fact that the requisite antibody of the invention selectively recognizes a shortened PTH peptide, CIP, while NOT binding to the longer CAP peptide: it must recognize the shorter peptide, and distinguish the longer one. Ultimately, both the written description and the enablement rejections seem to reduce to this issue,

which apparently underlies the Examiner's statement that "the existence of the antibody is unexpected."

When the previous response was prepared, the Applicant attempted to offer evidence that this selectivity pattern was well precedented, based on the Gao reference. However, the Applicant had misunderstood the Gao reference (specifically its reference to PTHrp 1-86) when drafting the response, and the Applicant initiated the telephonic interview that occurred on 10 February 2005 in order to correct this error prior to the Examiner's consideration of that response. While the Applicant greatly appreciates the Examiner's cooperation in conducting that interview, the Applicant believes that evidence of the state of the art with regard to the central questions about such selective antibodies has not been considered by the Examiner to date.

The Examiner's concern appears to focus on the selectivity pattern asserted for the antibody at issue, and the concern is understandable: the antibody of interest must distinguish between two species, *both of which by definition contain the portion of the peptide that the antibody recognizes*. The shorter peptide must contain the epitope to which the requisite antibody binds, else it could not be recognized by that antibody; and the longer peptide simply adds amino acids, so it still includes the portion of the shorter peptide that the antibody recognizes. Yet the invention requires an antibody that binds to the shorter peptide and distinguishes it from the longer one.

As the Examiner points out, the particular selective antibody of the invention is not well known in the literature: if it were, the present invention might not be new and patentable. But of course, as the specification demonstrates, many antibodies to PTH peptides *were* well known before the application was filed, and methods for producing antibodies against PTH and fragments of PTH were routine. The only real issue is obtaining one with the right selectivity. The Examiner appears to impose a standard that prevents such an antibody or assay from being patented until it is produced: that would be an extraordinary departure from U.S. patent law, and it is particularly surprising to encounter such a high standard in antibody technology, which the courts have recognized as being well developed and highly predictable (e.g., the *Noelle* court quoted the *Enzo* court when stating "the fact that the antibody technology is well developed and mature."

PTH is a peptide hormone. Like many other peptide hormones, it is part of a family of related peptides of varying lengths. Regulation of the activity of many of these hormones is achieved by starting with an inactive 'pro-hormone'; cleaving residues to make the active hormone when more of it is needed; and cleaving more residues to inactivate the hormone when less of the active hormone is needed. One of ordinary skill at the time the application was filed would have been aware of the state of the art for immunoassays and antibodies to these other peptide hormones; thus the availability of the desired selectivity pattern in other peptidyl hormones prior to the filing of the application should demonstrate that one of ordinary skill would expect the same selectivity pattern to be achievable in the PTH family. The following references demonstrate that *precisely the selectivity pattern required for the antibody of the invention* was well known among antibodies that bind to other peptides, including peptide hormones, prior to the filing date of the application.

The angiotensins are small peptide hormones that regulate blood pressure and affect other physiological processes as well. Like PTH, angiotensin peptides of various lengths are present in the blood stream, and the different forms have different effects. Thus it is useful to have assays that can distinguish each form. Dominique Simon, et al., published an article (the Simon reference) entitled, "*Direct, Simplified, and Sensitive Assay of Angiotensin II in Plasma Extracts Performed with a High-affinity Monoclonal Antibody*" that describes antibodies selective for angiotensin II (Ang II), in plasma that also contains angiotensin I, which is longer by two residues. *Clinical Chemistry* 38(10), 1963-67 (1992) **[Exhibit A]**. The authors describe methods to produce the selective antibody required, and demonstrate that it selectively binds to Ang II, an 8-residue peptide. They also demonstrate that binding drops sharply when a single amino acid is added to one end of the peptide forming Ang (1-9) (see Figure 1 on pg. 1965: this is not one of the natural forms); and binding drops still more when a second residue is added to form Ang I (a 10-residue peptide).

The Simon article was published in 1992, and the Simon antibody exemplifies the same selectivity pattern needed for the antibody of the invention: the antibody binds tightly to a shorter peptide, but distinguishes a longer version of the same peptide. The Simon antibody demonstrates that such selectivity is achievable in a peptide hormone, even where the longer peptide that must be distinguished is longer *only by a single amino acid.* The antibody required for the present invention

must recognize PTH 7-84 without binding to the longer PTH 1-84; thus it must recognize the shorter peptide and distinguish the longer one, and the difference between the two is much larger than the difference between Ang I and Ang II.

A more recent paper describes polyclonal antibodies used to determine Ang II levels, and states that the antibody used "cross-reacts with Ang III but has negligible cross-reactivity with Ang-I under assay conditions." V.Z.C. Ye, et al., *Clinical Science*, 98, 57-64 (2000) **[Exhibit B]**. Like the Simon antibody, this reference reports an antibody that binds the shorter peptides Ang II and II and distinguishes a slightly longer form of the same peptide—but here it is a polyclonal antibody rather than the monoclonal antibody reported in Simon.

Insulin is another peptide hormone that is synthesized in an inactive form, then gets clipped by proteases into an active form. Like the angiotensins and the PTH family, these are of obvious medical interest, and assays selective for insulin, or proinsulin, or both are valuable for research and for diagnostic purposes. P.M. Clark, et al., provide a review of the many different assays then available to measure levels of insulin and the proinsulin forms. *Ann. Clin. Biochem.* 36, 541-64 (1999) **[Exhibit C]**. As Tables 1 and 2 in Clark demonstrate, many different antibody assays for detection of insulin had been published and commercialized by 1999, and many were selective for insulin over the pro-forms. For example, in Tables 1 and 2, there are several antibodies that bind well to insulin but show little or no affinity for the proinsulin forms referred to as the '31,32 split' or the '32,33 split'. The insulin / proinsulin analogy is complicated by the fact that intact proinsulin includes a loop region that connects to insulin at two points. Selectivity for insulin over the intact proinsulin may thus be less persuasive, though it is certainly still relevant. However, each of these 'split' proinsulin forms is an insulin analog having additional amino acid residues added to one end. The observed selectivity patterns are thus directly analogous to that required for the antibody of the present invention. Also interesting for our purposes, there are numerous assays for "C-peptide", which is a peptidyl fragment that gets clipped off of proinsulin during activation, and many of these have very low affinity for proinsulin. Each of these numerous antibodies recognizes a shorter peptide and distinguishes the longer one.

Several papers also discuss antibodies selective for renin that distinguish it from its longer precursor, prorenin. Renin is an enzyme rather than a hormone, and prorenin has 43 extra residues at the N-terminal end that are clipped off by an activating enzyme. F.H.M. Derkx, et al., Clinical Chemistry, 42(7), 1051-63 (1996) **[Exhibit D]** (e.g., see pg. 1052: "monoclonal antibodies that are specific for rennin have recently become available.") W.M. Zuo, et al., Hypertension, 19, 249-254 (1992) **[Exhibit E]** (abstract: describing monoclonal antibody R1-20-5 which is specific for human active renin: "This antibody does not bind prorenin in human plasma..."). See also Circulation, 96, 220-26 (1997) **[Exhibit F]** (using the same antibody, R1-20-5). Thus the change in that case is more substantial than in the PTH subject matter at hand. Nevertheless, these references further demonstrate that before the present application was filed, it was already well known that antibodies could be obtained that would selectively bind to a shorter peptide in the presence of a longer version of the same peptide.

These references show that the selectivity of the antibody described in the application was technically feasible when the application was filed. More importantly, they demonstrate that one of ordinary skill reading the application when filed would reasonably understand that the applicant had "possession of the claimed invention", because it was well known in the art for a number of peptides of various sizes, that an antibody could be obtained that would recognize a shorter peptide while distinguishing a longer version of the same peptide. Moreover, the Angiotensin references demonstrate that an antibody to a peptide antigen can effectively distinguish a homologous peptide that is only one residue longer than the antigen. If the Examiner's comment that 'the existence of the antibody is unexpected' refers to an assumption by the Examiner that the selectivity pattern required for the antibody of the invention is unprecedented or even unusual, the above references should adequately rebut that assumption.

The Applicant regrets not presenting these references earlier: as explained during the telephonic interview, the Gao reference was believed to provide adequate support for this selectivity pattern when the prior response was prepared, so no further support was sought at that time. Once the Applicant recognized the mistake, the Applicant immediately informed the Examiner and effectively withdrew the Gao reference from consideration. Now the Examiner is asked to

reconsider the rejection in light of the evidence that antibodies having the selectivity pattern required for the invention were well known in the art before the application was filed.

During the telephonic interview on 10 February 2005, the Examiner indicated that it could be helpful to show that the antibody described in the D'Amour reference was produced prior to the application date. The inventor on the present application is an author on the D'Amour publication, which was published well after the filing date of this application. The application was filed on August 10, 2001 and claims priority to provisional application 60/224,447, which was filed August 10, 2000, while the D'Amour reference was published in 2003. (The footnote indicates that it was accepted for publication on August 29, 2003.) We are providing a declaration from the inventor **[Exhibit G,** supported by **Exhibit H]** stating that the T-PTH antibody of the D'Amour reference, which exhibits a selectivity pattern potentially similar to that of the disclosed invention, was produced before this application was filed. However, the selectivity characteristics described in the D'Amour reference were not recognized until after the application was filed.

The D'Amour publication describes a novel form of hPTH that was not fully characterized, and shows that an antibody assay referred to as the T-PTH assay could distinguish the novel form of PTH from 'normal' hPTH. The novel form of hPTH is detected by immunoassays that detect both the N-terminal portion of PTH (e.g. the CA-PTH assay which binds to the first four residues: see pg. 2038, first col.) and the C-terminal segments of PTH (the C-PTH assay, which binds to the PTH 69-84 fragment—see pg. 2043, first col.). The T-PTH assay as described in D'Amour detects both hPTH (PTH 1-84) and PTH 7-84, but does not bind to the novel form of hPTH. The authors suggest that it is likely that the new variant has the intact sequence of PTH, since both ends seem to be present. Yet it is not detected by the T-PTH assay, which detects PTH 7-84, which is seemingly a shorter peptide. This suggests that the T-PTH assay antibody has a selectivity pattern potentially similar to that of the antibody described in the present application.

The D'Amour authors point out that the immunoassay characteristics of the new variant of PTH do not fully characterize its structure. However, they do rule out at least some of the alternative explanations for their observations. They demonstrate that the novel form of hPTH

differs from chemically oxidized forms of PTH 1-84 and PTH 7-84. D'Amour, pg. 2043, first col. And they show close similarity of the novel form of hPTH to both hPTH and PTH 7-84 in polarity. This is apparent from the HPLC characteristics of the novel form of hPTH. It was not resolved from hPTH using previous HPLC conditions, but was resolved in this work by using "a more efficient acetonitrile gradient". In the improved conditions, the novel form of hPTH eluted at positions 42-43 of the chromatography, while hPTH eluted at position 45 and PTH 7-84 eluted at position 39. D'Amour, pg. 2041, second col. The novel form of hPTH thus exhibits polarity under the HPLC conditions that is intermediate between hPTH and PTH 7-84, suggesting that it is structurally similar to these species. The authors discuss the possibility that it is a phosphorylated form of PTH, see pg 2043, first col., but do not discuss whether that would be consistent with the HPLC behavior of the novel form of hPTH.

One reasonable explanation for this data is that the novel form of hPTH includes the full amino acid sequence of hPTH, but adopts a conformation that conceals the epitope that is recognized by the T-PTH assay. This would explain its immunological reactivity pattern. In that case, the T-PTH antibody would be exhibiting the same selectivity pattern as the antibody described in the application: it would be recognizing a shorter peptide, PTH 7-84, while distinguishing the longer novel form of hPTH that contains the same epitope sequence as the recognized species.

The Rejection under 35 U.S.C. § 112 first paragraph: Enablement.

The Examiner also rejects the claims as not adequately enabled. The Examiner asserts that "these antibodies are not well known in the art and thus one of ordinary skill in the art would have a low level of predictability in the art," and "there are no working examples providing an antibody which distinguishes a peptide sequence for CIP that present an epitope available for antibody binding in CIP, but does not bind to this same peptide sequence in cyclase activating parathyroid hormone". The Examiner further asserts that "the art is unpredictable", so that one skilled in the art cannot practice the claimed invention without undue experimentation.

First, to establish a case for non-enablement, the Examiner is required to provide "acceptable reasoning inconsistent with enablement." In re Strahilevitz, USPQ 561, 563 (CCPA

1982). The *Strahilevitz* court reiterated that a working example is not required to provide enablement, so the absence of a working example is not "inconsistent with enablement." An assertion that the described antibody is novel cannot provide "acceptable reasoning" to defeat patentability, either; if it did, a working example would be a requirement for patentability of any novel invention. And an unsupported and unspecific assertion that "the art is unpredictable" cannot satisfy the requirement for 'acceptable reasoning', either.

The standard for enablement is whether one of ordinary skill could practice the claimed invention without undue experimentation. As the Examiner states, the factors that must be considered in determining undue experimentation are set forth in *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988). The decision on whether undue experimentation would be required involves consideration and balancing of at least the following factors:

(1) The nature of the invention. The invention relates to an antibody assay method: the courts and the PTO have stated that "antibody technology is well developed and mature". Synopsis of PTO Guidelines on Written Description, at 59-60. Furthermore, the invention relates to an antibody assay to measure forms of a peptide, PTH: antibodies to PTH, and to many peptides similar to PTH, were very well known by the time the application was filed, as evident from the references provided above and those cited in the specification. The insulin reference by Clark, for example, was published in 1999, and is a review listing dozens of published and *commercialized* antibody-based assays for forms of insulin.

(2) The state of the prior art. As the references discussed above demonstrate, it was well known at least by 1992 that the selectivity pattern of the claimed assay could be achieved by antibodies, specifically antibodies to a peptide: it was known that antibodies to a peptide hormone could recognize one such peptide and could distinguish a longer version of the same peptide *differing by as little as a single amino acid.*

(3) The predictability or lack thereof in the art. The Examiner asserts that the art is unpredictable, presumably in reference to the particular selectivity pattern of the requisite antibody.

However, the references discussed herein rebut that assertion. They demonstrate in several closely related systems, all peptides, that it is routinely possible to produce antibodies that bind to one peptide and distinguish it from longer peptides. The reported systems include peptides both shorter and longer than PTH; and certainly there is ample precedent for antibody production using PTH and fragments of PTH as the antigen. Identification of a suitable antigen for practicing the invention then is reduced to a routine screening process using the described and available CAP and the antibodies produced against the described and available antigen, CIP. See, e.g., D'Amour at page 2038, stating that the hPTH 1-84 and hPTH 7-84 used, as well as several other PTH fragments, were "purchased from BACHEM."

(4) The amount of direction or guidance presented. Because antibody technology in general is so well developed and mature, little guidance is necessary for the production of an antibody to PTH 7-84. Those skilled in the art could produce as many different antibodies to this peptide as needed with no additional guidance; indeed, the literature provides ample evidence of the ease with which antibodies are generated against various PTH fragments. The unique twist here is the particular selectivity pattern, which is not reported with PTH antibodies. However, the specification provides guidance on a screening process for selection of an antibody having this selectivity pattern. Specification at pg 9. This screening step may be less common than the production of antibodies, but, as the cited references indicate, demonstrating selectivity between two closely related species is well precedented in the art, and the application provides specific guidance on a systematic screening method as well.

(5) The presence or absence of working examples. The Examiner asserts that there are no working examples. Even if correct, this is only one factor to consider. The MPEP (see § 715.07 describing filing of an application as constructive reduction to practice) make it clear that an applicant does not have to reduce an invention to practice—as does the *Wands* case itself, which clearly identifies this as only one factor to be considered.

(6) The quantity of experimentation necessary. That which is well known in the art need not be included in a patent application, and indeed it is preferably omitted. Thus there is no

need for much description of the methods for producing antibodies to PTH fragments. The application provides guidance on the less commonly practiced screening process to select an antibody that expresses the desired selectivity pattern.

According to the *Wands* court, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.* at 1404. Here, clearly the production of antibodies raised against PTH fragments is routine; and with the screening guidance provided in the specification, the selection of an antibody having the required selectivity pattern should also be a routine matter for one skilled in the art.

(7) The relative skill of those in the art. The antibody arts are considered well developed and mature; indeed, the *Wands* decision relates to an *immunoassay method using monoclonal antibodies*, and the court stated that "There was a high level of skill in the art at the time when the application was filed…"—and the *Wands* decision was issued in 1988! Those 'skilled in the art' at the time this application was filed (2000 for the provisional, and 2001 for the utility application) were capable of routinely producing and testing both monoclonal and polyclonal antibodies. All of the cited references demonstrating the feasibility of the selectivity pattern of interest predate the filing date of the utility application: one was published in 2000, the same year the provisional application was filed, and all the others predate even the provisional application.

(8) The breadth of the claims. The claims are very narrowly drawn, focusing on a single antigen and on selectivity over a single longer peptide.

A *Wands* analysis involves balancing all of the factors to determine whether 'undue' experimentation would be required for one of ordinary skill to practice the claimed invention. Here,

the invention is in a field long recognized as well-developed and mature;

the level of skill in the art is recognized as being quite high;

the literature references show that it was reasonably predictable that an antibody having the required selectivity pattern could be obtained;

most of the work involved would be routine production of antibodies to a protein antigen that is described by structure;

guidance was provided for the necessary screening process to identify the desired selective antibody;

and the peptide to be distinguished is available and is described by its structure.

Thus on balance, the absence of a working example, while a factor to be considered, cannot outweigh the other factors that support the conclusion that the claimed invention was enabled as of the filing date. At least for the narrow claims presented here for consideration, one skilled in the art could generate many antibodies against CIP and could readily screen them for the ability to distinguish CIP using a method such as that described in the application; upon doing so, one would reasonably expect to find an antibody that provides the selectivity pattern described in the application. The required experimentation would be routine, the CIP and CAP required are fully described and readily available, and based on the guidance provided and on references such as Exhibits A-F, the skilled practitioner would know how to proceed and would reasonably expect to succeed.

In view of the above, each of the presently pending claims in this application is believed to be in condition for immediate allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 532212001500. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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